Citric acid-based elastomers provide a biocompatible interface for vascular grafts

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Abstract: Prosthetic vascular bypass grafting is associated with poor long-term patency rates. Herein, we report on the mid-term performance of expanded polytetrafluoroethylene (ePTFE) vascular grafts modified with a citric acid-based biodegradable elastomer. Through a spin-shearing method, ePTFE grafts were modified by mechanically coating a layer of poly(1,8 octanediol citrate) (POC) onto the luminal nodes and fibrils of the ePTFE. Control and POC-ePTFE grafts were implanted into the porcine carotid artery circulation as end-to-side bypass grafts. Grafts were assessed by duplex ultrasonography, magnetic resonance angiography, and digital subtraction contrast angiography and were all found to be patent with no hemodynamically significant stenoses. At 4 weeks, POC-ePTFE grafts were found to be biocompatible and resulted in a similar extent of neointimal hyperplasia as well as leukocyte and monocye/macrophage infiltration as control ePTFE grafts. Furthermore, POC supported endothelial cell growth. Lastly, scanning electron microscopy confirmed the presence of POC on the ePTFE grafts at 4 weeks. Thus, these data reveal that surface modification of blood-contacting surfaces with POC results in a biocompatible surface that does not induce any untoward effects or inflammation in the vasculature. These findings are important as they will serve as the foundation for the development of a drug-eluting vascular graft.

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Key words: ePTFE; prosthetic; bypass graft; polymer; endothelial cell; neointimal hyperplasia

INTRODUCTION

Peripheral arterial disease (PAD) is a debilitating and disabling sequela of atherosclerosis. PAD is estimated to affect 8 million Americans and the prevalence is growing with the large increase of the aging population.1 For patients with severe PAD, lower extremity bypass grafting often remains the only option for limb salvage. The gold standard conduit for infrainguinal bypass grafting is autologous vein. Although the patency for infrainguinal vein grafts remains ~70% at 5 years,2 vein may not be available due to intrinsic venous disease or prior vein harvesting. In these cases, expanded polytetrafluoroethylene (ePTFE) grafts are the most commonly used alternative bypass conduit. However, the primary patency rates for infrapopliteal ePTFE bypass grafts are dismal. For example, when used in femoral-popliteal bypass grafting, the 3- and 5-year patency rates for ePTFE grafts are only 64% and 44%.3 When used for infrapopliteal bypass grafting, the 1-, 2-, and 4-year patency rates for ePTFE grafts are 65%, 30%, and 12%, respectively.4

The etiology of long-term prosthetic bypass graft failure is commonly due to the development of neointimal hyperplasia at the distal anastomosis.5–8 For some time now, surgeons have attempted to mitigate the problem of graft thrombosis with the oral administration of anticoagulant and anti-inflammatory drugs.9 Furthermore, because of the lower long-term patency rates observed with prosthetic bypass grafting, surgeons have also developed intraoperative
approaches to improve graft patency. These modifications are largely intended to decrease the compliance mismatch between the prosthetic graft and the native artery and include vein cuffs, vein patches, vein boots, and arteriovenous fistulas at the distal anastomosis. However, despite these pharmacologic and surgical improvements, patency rates remain dismal, especially when the distal outflow is at or below the level of the popliteal artery. Thus, many researchers are investigating alternative strategies that involve surface modification of the graft’s lumen to obtain a localized beneficial effect, thereby avoiding systemic side effects. To date, modifications of prosthetic grafts have been designed to present a more antithrombogenic surface, slowly release a drug, stimulate in vivo graft endothelialization, or improve the retention of water and freeze-dried for storage. The prepolymer was purified by precipitation in acid and 1,8-octanediol were melted together at 160°C. The mixture was stirred for 15 min. The temperature was subsequently decreased to 140°C and the mixture was stirred for 1 h. The prepolymer was purified by precipitation in water and freeze-dried for storage. The prepolymer was soluble in ethanol or 1,4-dioxane, which are less toxic than other commonly used solvents.

Surface modification of the ePTFE graft with POC

The lumen of thin-wall stretch ePTFE grafts (6 mm inner diameter, Gore-Tex, W. L. Gore & Associates, Flagstaff, AZ) was modified by mechanically coating a POC layer onto the nodes and fibrils of ePTFE through a spin-shearing method as previously described. Briefly, a 5 mm diameter glass rod was dipped into 10% POC prepolymer (pre-POC) solution in 1,4-dioxane and inserted horizontally into the motor of a mechanical stirrer (IKA-Werke GmbH & Co. KG, Eurostar ST P CV PS S1, Staufen, Germany). The pre-POC-coated glass rod was spun clockwise at 300 rpm for 2 min and an 8 cm long piece of ePTFE graft was placed concentrically over the spinning rod. The lumen of the graft was sheared against the spinning rod for 2 min by manually rotating the graft counterclockwise. The above procedure was considered to be one coating. To change the amount of POC deposited onto the graft, the above procedure was repeated three times (defined as three coatings). After air-drying, the pre-POC-coated ePTFE graft was put into an oven at 80°C for 2 days to obtain POC-ePTFE grafts. Grafts were sterilized via ethylene oxide exposure and degassing according to the manufacturer’s instructions.

Presurgical care and anesthesia

All animal procedures were performed by use of aseptic technique in accordance with the Northwestern University Animal Care and Use Committee. Domestic juvenile castrated male Yorkshire-Landrace pigs (Oak Hill Genetics, Ewing, IL) weighing 25–30 kg were utilized. Animals received antibiotic prophylaxis with one dose of cefazolin (25 mg/kg intramuscular [IM]) preoperatively and postoperatively. Aspirin (325 mg oral [PO]) was administered daily starting 5 days before surgery and continued throughout the entire postoperative course. On the day of surgery, the animals also received an aspirin suppository (325 mg).

Preoperative analgesia and sedation included buprenorphine (0.01 mg/kg IM), acepromazine (0.15 mg/kg IM), ketamine (20 mg/kg IM), and atropine (0.05 mg/kg IM). After intubation, anesthesia was maintained with inhaled isoflurane (0.5–2.0%) delivered with 100% oxygen. Temperature, heart rate, respiratory rate, and oxygen saturation were monitored continuously and recorded every 15 min throughout the procedure.

Surgical procedure

Details of the animal model have been previously published. Briefly, animals were placed in the supine position, and their necks were shaved then prepped with betadine and alcohol (70%). Pigs received bilateral ePTFE bypass grafts (n = 5). Through a midline neck incision,
both right and left common carotid arteries (CCA) were exposed. Following heparin (150 U/kg intravenous [IV]) administration, the right CCA was occluded proximally and in the midsection with noncrushing vascular clamps. A longitudinal arteriotomy was made, and a 6 cm length of PTFE graft (6 mm thin wall stretch ePTFE, Gore, Flagstaff, AZ) was anastomosed in an end-to-side fashion with running 6-0 polypropylene suture. Care was taken to ensure that the ePTFE graft was anastomosed at a 45° angle with respect to the native artery, thereby dictating a standard arteriotomy length. Before completion of the proximal anastomosis, the native vessel was flushed and irrigated with heparinized saline (2000 U heparin per 1 L normal saline). After completion of the proximal anastomosis, flow was restored in the CCA for 5 min while the graft was clamped near the anastomosis. Next, the right CCA was occluded distally and in the midsection with noncrushing vascular clamps. The distal anastomosis was created in a manner similar to the proximal anastomosis. Just before its completion, the graft and native artery were vigorously flushed with heparinized saline. Once the distal anastomosis was completed, the distal arterial clamp was removed, restoring blood flow to the CCA through the ePTFE graft. The midsection vascular clamp was replaced with double ligation using 2-0 silk suture to simulate an occlusion. After completion of the right bypass graft, a second dose of heparin (75 U/kg IV) was administered, and the left bypass graft was created in a similar manner. After both bypass grafts were completed, meticulous hemostasis was achieved, and the incision was closed in multiple layers using absorbable suture. Animals were monitored until awake, alert, and sternal. Postoperative analgesia consisted of buprenex (0.01 mg/kg IM) given every 12 h for the first 48 h postoperatively.

**Magnetic resonance angiography**

Magnetic resonance angiography (MRA) was performed to evaluate graft patency 3 weeks postoperatively. After sedation with acepromazine (0.15 mg/kg), atropine (0.05 mg/kg), and ketamine (20 mg/kg), intubation was performed and anesthesia was maintained with inhaled isoflurane (1–2%) delivered with 100% oxygen. MRA was performed using a time-resolved T1-weighted gradient echo pulse sequence. A time-series of 3D contrast-enhanced images were acquired with a gadolinium-based contrast agent (0.1 mmol/kg IV; Magnevist, Berlex, Princeton, NJ). Noncontrast angiograms were also performed using a time-of-flight imaging protocol.

**Duplex ultrasonography**

Four weeks postoperatively, just before sacrifice, both ultrasonography and contrast angiography were conducted. Following exposure of both the right and left CCA and bypass grafts, intraoperative duplex ultrasonography was performed, obtaining B-mode images and Doppler velocity measurements including peak systolic velocity (PSV) and end diastolic velocity (EDV). For each side, measurements were obtained at the proximal CCA, proximal anastomosis, proximal graft, mid-graft, distal graft, distal anastomosis, and distal CCA. A significant stenosis was defined as PSV greater than two times the normal inflow artery velocity.

**Contrast angiography**

After assessing the grafts with duplex ultrasonography, digital subtraction contrast angiography was performed percutaneously by accessing the common femoral artery and placing a 5 French (F) introducer sheath. Using a 0.035" J-wire, a 5 F multisided-hole catheter was advanced into the aortic arch under fluoroscopy. An arch angiogram was obtained with contrast injection (20 mL, Omnipaque, Amersham, Piscataway, NJ) through the catheter. Each CCA was selected using an angled guide catheter and the J-wire, and angiograms were obtained of both CCA and ePTFE grafts using 10 mL of contrast media. Following angiogram completion, the animals were euthanized with pentobarbital (72 mg/kg).

**Tissue processing**

The ePTFE bypass grafts and native artery extending 2 cm from each anastomosis were harvested en bloc and underwent ex vivo perfusion-fixation in 10% buffered formalin for 12 h. Next, the samples were dehydrated with a graded ethanol series (70%, 95%, 100%), followed by xylenes, then cut into 1 cm sections, and placed in plastic tissue cassettes (Tissue-tek, Hatfield, PA). The samples were embedded in paraffin, and blocks were cut into 5 μm transverse sections and the sections were transferred onto slides.

**Tissue staining and morphometric analysis**

Sections were examined histologically for evidence of neointimal hyperplasia using routine Hematoxylin and Eosin (H&E) staining. Digital images were collected with light microscopy using an Olympus BHT microscope (Melville, NY). Five equally-spaced sections throughout each proximal and distal anastomoses were analyzed for each bypass graft. Neointimal hyperplasia (area in millimeters) under the ePTFE graft was assessed using ImageJ software (National Institutes of Health, Bethesda, MD) and adjusted according to the circumference length of ePTFE on each cross section. To accurately compare the degree of neointimal hyperplasia from each anastomosis, the angle of embedding and cutting the block with respect to the angle of the ePTFE to the native artery was accounted for and controlled so that each block was similar, as changes to the block orientation can artificially underestimate or overestimate the degree of neointimal hyperplasia.

**Immunohistochemistry**

For immunohistochemistry, 5 μm-thick sections were deparaffinized in xylenes and rehydrated in graded alcohol.
For the antigen retrieval process (required for detection of anti-human von Willebrand factor and mouse monoclonal MAC387), specimens were treated in a heated citrate buffer solution, pH 6.0 (Lab Vision, Fremont, CA) for 20 min. Immunohistochemistry was carried out using the HRP Polymer & DAB Plus Chromogen Ultravision LPValue Detection System (Thermo Scientific, Fremont, CA). Endogenous peroxidase activity was blocked by incubating the slides in a hydrogen peroxide blocking reagent (provided in kit) for 15 min. To block nonspecific background staining, specimens were incubated in Ultra V Block (provided in kit) for 10 min. Endothelial cells were detected with polyclonal rabbit anti-human von Willebrand factor (1:200, DAKO, Glostrup, Denmark) for 30 min at room temperature. Leukocytes were detected with purified mouse anti-pig CD45RA monoclonal antibody (1:200, BD Biosciences Pharmingen, San Jose, CA) for 60 min at room temperature. Macrophages/monocytes were detected with the mouse monoclonal MAC387 antibody (1:200, Abcam, Cambridge, MA) at 4°C overnight. Specimens were then incubated in DAB Plus Chromogen and DAB Plus Substrate (provided in kit) for 3 min. Counterstaining was performed with Gill 2× Hematoxylin (Protocol, Fisher Scientific, Waltham, MA). For negative controls, antibody was omitted. To objectively assess the extent of monocyte and macrophage infiltration between groups, positive staining nuclei were counted in four high power fields per each section.

Scanning electron microscopy (SEM)

Graft sections were fixed, dehydrated, and sputter-coated with gold before imaging on a Hitachi 3500 N at the EPIC facility of Northwestern University.

Statistical analysis

Results are expressed as mean ± standard error of the mean. Differences between multiple groups were analyzed by use of one-way analysis of variance with the Student-Newman-Keuls post hoc test for all pairwise comparisons.
Differences between two groups were analyzed with the Student’s t-test (SigmaStat, SPSS, Chicago, IL). Statistical significance was assumed when $p < 0.05$.

**RESULTS**

POC is nonthrombogenic and biocompatible in the vasculature at 28 days

Five adult male Yorkshire-Landrace pigs underwent bilateral ePTFE bypass grafting, each with a control ePTFE (right) and POC-ePTFE (left) bypass graft. At 21 days, all bypass grafts in both treatment groups were patent as assessed by MRA [Fig. 1(A)]. At 28 days, all bypass grafts in both therapy groups were patent as assessed by 2D subtraction contrast angiography [Fig. 1(B)], and duplex ultrasonography [Fig. 1(C)]. No significant stenoses were identified on any of the three imaging modalities. Furthermore, using duplex ultrasonography, peak and end diastolic velocities were obtained throughout the bypass grafts as well as in the proximal and distal native artery. No statistically significant differences were found between the velocities within each graft, as well as between the control and POC-ePTFE grafts (Table I). Following graft procurement, the proximal and distal anastomoses of the bypass grafts were assessed for the development of neointimal hyperplasia. POC-ePTFE grafts developed a similar degree of neointimal hyperplasia when compared with the control ePTFE grafts (Fig. 2), confirming the biocompatibility of POC.

POC is present at 28 days

As POC is known to be biodegradable over time, we assessed the bypass grafts for the presence of POC on the ePTFE after being in the circulation for 28 days. Following graft procurement, midsections of the graft were assessed using SEM. In control ePTFE grafts, the characteristic nodal and fibril distribution is seen, as well as scattered fibrous coagulum [Fig. 3(A)]. In grafts coated with POC, SEM images reveal residual POC coating, which was visible within a few cell-free areas of the graft [Fig. 3(B)]. Thus, the POC synthesis conditions used in this study do not lead to complete degradation within 4 weeks in the circulation.

POC supports endothelialization in vivo

After graft harvesting, grafts from both treatment groups were assessed immunohistochemically for the presence of endothelial cells. POC supported endothelialization throughout all sections analyzed [Fig. 4(B)]. This endothelialization continued into the lumen of the graft material, far from the native artery. To further support this assessment, small sections of the graft material were processed for SEM. SEM confirmed the presence of an intact endothelial cell monolayer on both control and POC-coated ePTFE bypass grafts [Fig. 4(C)].

POC does not induce inflammation in vivo

Immunohistochemical assessment of the anastomoses revealed similar patterns of CD45 positive leukocytes in control and POC-coated ePTFE bypass grafts [Fig. 5(A,B)]. In the native artery opposite the anastomosis, a similar degree of leukocyte infiltration was also observed between the two treatment groups [Fig. 5(C,D)]. With respect to monocyte and macrophage infiltration, a similar pattern was observed between the control and POC-ePTFE grafts; however, greater overall monocyte/macrophenage infiltration was observed in both treatment groups when compared with that observed with leukocytes. A similar extent of monocyte and macrophage infiltration was observed in the neointima [Fig. 6(A–D)] and in the ePTFE graft material between the two

<table>
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<tr>
<th>Section</th>
<th>Control</th>
<th>Control EDV</th>
<th>POC-ePTFE</th>
<th>POC-ePTFE EDV</th>
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<tr>
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<td>Mean ± SE</td>
<td>Mean ± SE</td>
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<td>1.674 ± 0.24</td>
<td>0.278 ± 0.09</td>
<td>0.293 ± 0.07</td>
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PSV, peak systolic velocity; EDV, end diastolic velocity; m/s, meters per second; SE, standard error; P, NS between treatment groups.
treatment groups [Fig. 6(E,F)]. Of note, infiltration of monocytes and macrophages into the prosthetic material was commonly observed in both treatment groups, whereas CD45 positive leukocytes were not observed in the interstices of the graft material.

**DISCUSSION**

The ideal prosthetic graft should be nonthrombogenic, hemo- and bio-compatible at high and low shear stresses, have similar compliance to native vessels, and inhibit the development of neointimal hyperplasia. As the majority of new biomaterials have failed to replicate the mechanical and biological properties of blood vessels, researchers have turned to surface modification approaches to improve the safety and efficacy of current intravascular devices. Unlike other surface modification techniques, POC modification of ePTFE does not involve exposure to plasma glow discharge or other harsh solvent treatments. Mechanical spin shearing is able to comprehensively coat the nodes and fibrils within the ePTFE graft lumen. We have previously reported the *in vitro* and short-term hemocompatibility characterization of POC.\textsuperscript{16,19} Furthermore, the modification of ePTFE grafts with POC improved endothelial cell adhesion, reduced platelet adhesion *in vitro*, and did not affect graft compliance.\textsuperscript{16,21} In the study described herein, we hypothesized that the mechanical and interfacial properties of POC would make it a viable candidate material for the surface modification of vascular grafts. Although the exact mechanisms for these characteristics are under study, the possibility to use POC as a base material to engineer a functional endothelium *in vitro* and/or locally deliver drugs in the vasculature prompted a longer term evaluation of its intravascular biocompatibility.

![Figure 2.](image1.png) **Figure 2.** POC-ePTFE grafts produce a similar amount of neointimal hyperplasia when compared with control ePTFE grafts. A: Quantification of neointimal hyperplasia at the proximal anastomosis (PA) and distal anastomosis (DA) of the control ePTFE and POC-ePTFE bypass grafts. B: Hematoxylin and eosin stained cross sectional images of control ePTFE and POC-ePTFE bypass grafts at the PA and DA. Arrows indicate neointimal hyperplasia. Arrowheads indicate the graft material. 1× magnification. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

![Figure 3.](image2.png) **Figure 3.** The POC coating is still present on the ePTFE grafts at 28 days. Scanning electron microscopy of a mid-section of a A: control ePTFE and B: POC-ePTFE bypass graft harvested after 28 days in the porcine carotid artery circulation. Note the persistent POC coating on the POC-ePTFE bypass graft at 28 days as well as the characteristic nodal and fibril pattern of the ePTFE material. 50 μm scale bar.
Most studies that involve the surface modification of vascular grafts have focused on the potential thrombogenic characteristics of the blood-biomaterial interactions (for review, see 15). Other than a few studies of drug-eluting grafts, there is a dearth of literature on the characterization of thrombogenicity and neointimal hyperplasia of a biomaterial coating for vascular applications. Through a very systematic histological and functional characterization, this study confirms the nonthrombogenic nature of POC and a benign tissue response that did not lead to significant neointimal hyperplasia relative to control uncoated ePTFE grafts, the current standard of care. Blood velocity measurements were within the normal range and significantly below velocity values that are consistent with hemodynamically significant lesions. These findings represent a significant step forward for the intravascular use of this novel biodegradable material in humans, as the coated grafts were not associated with any negative tissue response. The animal model used was based on a previously established porcine model of prosthetic bypass grafting that results in reproducible neointimal hyperplasia.20

Figure 4. POC-ePTFE grafts support endothelialization. A: Schematic demonstrating how the bypass grafts were processed at the proximal and distal anastomoses for assessment of endothelialization. B: Immunohistochemical assessment of endothelial cell staining progressing from proximal-to-distal (A-to-F) for the proximal and distal anastomoses. Larger picture represents the whole image at 1× magnification. Smaller inset represents the endothelial cell layer at 40× magnification. C: Scanning electron microscopy of the lumen of the control ePTFE and POC-ePTFE bypass grafts demonstrating a continuous endothelial cell monolayer (arrows) on both the control ePTFE and POC-ePTFE grafts. Arrowheads indicate leukocytes. 50 μm scale bar. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Endothelialization is important for the long-term function of intravascular devices such as stents and vascular grafts. In fact, this point has been greatly emphasized with the recent data pertaining to drug-eluting coronary stents. Although early data was encouraging and demonstrated reduced rates of restenosis and late lumen loss, late results of drug-eluting coronary stents have been disappointing. Several pooled or meta-analysis studies have revealed either similar mortality or worse mortality with these drug-eluting stents when compared with bare-metal stents. This increased mortality appears to be secondary to an increased rate of in-stent thrombosis. The drug-eluting stents, while inhibiting vascular smooth muscle cell proliferation, are also inhibiting endothelial cell proliferation. As a result, the stent is not covered by endothelial cells and remains thrombogenic. It remains to be determined if the neoendothelium is functional. A functional endothelium is critical to blood vessel homeostasis, angiogenesis, and overall function.

The inflammatory response to a permanently implanted intravascular device may determine its long-term function. We assessed whether POC stimulated or inhibited, relative to ePTFE, the induction of inflammation following prosthetic bypass grafting. Grafts were assessed immunohistochemically for the presence of CD45 positive leukocytes as well as for monocytes and macrophages using the MAC387 antibody. Inflammation and neointimal hyperplasia within the POC-ePTFE grafts was comparable to that of control-uncoated ePTFE grafts. The blood and vascular tissue response to POC is a significant improvement when compared with fibrin-coated ePTFE grafts that were also tested in a porcine animal model. The fact that POC does not enhance the inflammatory response induced by ePTFE suggests that it is a viable delivery platform for drugs designed to inhibit thrombosis and neointimal hyperplasia and/or promote in vivo endothelialization for this prosthetic material.

Lastly, our data suggested that POC was still present on the graft samples harvested at 4 weeks, indicating that it had not yet degraded. Depending on the degree of crosslinking, choice of diol, and the inclusion of nanopores, poly(diol citrates) may degrade on a timescale ranging from weeks to...
years. For the crosslinking conditions used, one would expect a 20–25% degradation based on in vitro degradation profiles. It is difficult, if not impossible, to accurately evaluate the extent of POC degradation in vivo in this animal model; nevertheless, our data confirm that there are no untoward tissue responses to POC relative to native ePTFE. Over time, one would expect a foreign body response that is in line with that caused by only having ePTFE present at the intervention site.

In conclusion, this study describes the blood and vascular tissue response to poly(diol citrate)-coated

Figure 6. POC-ePTFE grafts do not increase monocyte/macrophage infiltration. Immunohistochemical analysis for monocytes/macrophages (cells stained brown) using the MAC387 antibody in control ePTFE grafts (A, C, and E) and POC-ePTFE grafts (B, D, and F). Arrowheads denote interface between graft material and neointimal hyperplasia. Images were obtained with 40× magnification. (G) Objective assessment of MAC387 positive staining cells per high power field in the neointima and in the graft material. The differences between groups were not statistically significant. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
ePTFE vascular grafts. Poly(diol citrates) may offer a powerful platform for the simple modification of ePTFE vascular grafts in order to improve the safety and efficacy of revascularization procedures. By all measures in this study, the poly(diol citrate) coating did not elicit thrombosis, inflammation, or restenosis.

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